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DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/019,566

Applicant(s)

LINDHOLM, LEIF

Examiner

Maria B Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/31/01, 6/28/04.
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date. 12/04.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 9/17/04.

Claims 1-23 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-21 and 23 and SEQ ID NO:12) in the amendment filed 11/17/04 is acknowledged. Applicant's election with traverse of the restriction election in the reply filed on 11/17/04 is acknowledged. The traversal is on the ground(s) that as the instant application is a national phase application of an International PCT application, restriction practice under 35 USC 121 and its associated rules do not apply. Secondly, the examiner reviewing the PCT application did not require a sequence election. Furthermore, the office has made no showing that there is a lack of unity between the sequences. Applicants' feel that it is improper for the office to refuse to examine that which applicants regard as their invention unless the subject matter lacks unity. The sequences are grouped into amino acid linkers (SEQ ID Nos: 3-8), external trimerization motifs (SEQ ID NO:1-2) and survival sequences (SEQ ID NO:10-12). Each group has unity of invention. If the restriction requirement were maintained, applicants would never be able to have their invention fully examined on the merits as they have claimed it. Finally, from a public policy point of view applicants point out that this practice of sequence election puts a burden on the patent examination system and is contrary to the advancement of the arts.

This is not found persuasive because the Commissioner has established rules for Examination of Patent Applications Containing Nucleotide Sequences as taught in 1192 O.G. 68

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(November 19, 1996) because of the high burden placed on the Office to search sequences.

Applications comprising multiple sequences must include a selection of one sequence to alleviate the search burden and avoid a backlog of cases. The selection policy has furthermore been established because nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. In cases restricted based upon PCT Rules for Unity of invention, the Commissioner has established the following guidelines. "up to four (4) such additional sequences per group is a reasonable number for examination. Further, claims directed to the selected sequences will be examined with claims drawn to any sequence combinations, which have a common technical feature with the selected sequences. Nucleotide sequences encoding the same protein are considered to satisfy the unity of invention standard and will continue to be examined together." (see MPEP 1851). In the instant case, three groups of sequences have been recited, the first groups comprises five unrelated sequences encoding amino acid linkers (SEQ ID Nos: 3-8), the second two sequence encoding external trimerization motifs (SEQ ID NO:1-2) and the third three sequences encoding survival sequences (SEQ ID NO:10-12). In any one group, the sequences do not encode the same protein. Therefore, in addition to SEQ ID NO: 13, which is also subject to a sequence search, four of the sequences recited in the claims are under review. Therefore, the selection requirement for a single sequence form each group is still deemed proper and is therefore made FINAL.

In response to the restriction requirement, applicants had only elected a single sequence from the group encoding survival sequences in the response filed 11/17/04. In a telephone interview 12/6/04, applicants' have elected SEQ IN NO:6 from the group of sequences encoding amino acid linkers and SEQ ID NO: 1 from the group encoding external trimerization motifs.

Claim 22 was mistakenly omitted from Group I in the restriction requirement mailed 9/17/04. In fact, Group I should have comprised claims 1-23 as regards use of the adenovirus for treatment of disease *in vivo*. Claim 14 has been withdrawn as being drawn to non-elected subject matter. Therefore, claims 1-13 and 15-23 are under examination in this application.

Information Disclosure Statement

Information Disclosure Statements filed 12/31/01 and 6/28/04 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Specification

The title of the invention, Recombinant Adenovirus, is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Sequence Compliance

In order to put the instant application in sequence compliance, applicants have submitted a substitute sequence listing and computer readable format and a letter stating that the two are the same and comprise no new matter in a response filed 12/12/03. However, the substitute sequence listing is not associated with the file. Therefore, a replacement sequence listing is required.

Claim Objections

Claims 10, 16, 21 and 22 are objected to because of the following informalities: the claims recite non-elected subject matter and should be redrafted to delete the non-elected subject matter.

Claim 23 recites “fibergene” as one word when it should be two words, “fiber” and “gene”. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-13 and 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-13, 15, 16 and 18-21 are vague and indefinite in that the metes and bounds of “characterized in that” are unclear. It is unclear if the meaning of the term “characterized” is open (i.e. comprising) or closed (i.e. consisting of). Furthermore, use of the term “characterized in that” is indefinite as it fails to establish the metes and bounds of the adenovirus encompassed by the claimed language. It is unclear how closely related the adenovirus must be to the recited embodiments.

Claim 2 recites the limitation "said structural modification" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 6, 8 and 23 are vague and indefinite in that the metes and bounds of “restriction sites” are unclear. The claims recite that modifications occur at various restriction sites and, therefore, a reference sequence is required to practice the claimed invention. The specification teaches that the restriction sites are relative to the Ad5 genome. However, there is no reference sequence provided in the claims to know the exact sites of modification.

Claim 9 is vague and indefinite in that the metes and bounds of “an amino acid linker has been added” are unclear. It is unclear if the linker has been added relative to the native or substituted trimerization and cell

Claim 23 is vague and indefinite in that the metes and bounds of “subcloning” in step (a) and step (b) are unclear. It is unclear into what the fragments are subcloned as applicants simply state that the fragments are subcloned. Furthermore, it is unclear from where the fragments are subcloned.

Claim 23 is vague and indefinite in that the metes and bounds of “deletion of the native fibergene” are unclear. Applicants do not recite from where the sequences are deleted.

Claim 23 is vague and indefinite in that the metes and bounds of “coding for” are unclear. It is not clear to what “coding for” refers.

Claim 23 is vague and indefinite in that the metes and bounds of “construct under (c)” are unclear. As the fragment in (c) appears to code a recombinant fiber, it is unclear how the recombinant fiber can be ligated onto itself. Furthermore, it is unclear exactly what a “construct under (c)/(d)” is denoting. It is not clear to what the construct is “under”.

Claim Rejections - 35 USC § 112, first paragraph

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 8, 12, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants recite a genus of adenovirus with modifications occurring in relation to specific restriction sites.

Applicants recite a broad genus of fragments of T-cell receptors and of monoclonal antibodies.

Applicants recite a broad genus of sequences, which increase the survival of the fiber in the cytosol of infected cells thereby enhancing transportation into the nucleus.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The claims recite a modified adenovirus in which the sites of modifications are described in relation to restriction sites. According to the specification, the sites correlate to the restriction

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map of adenovirus subtype 5 (Ad5). For example, a new cell-binding ligand is introduced between restriction sites NheI and HpaI in the fiber shaft (claim 6), shaft repeats downstream of HpaI are removed (claim 8) and a series of deletions and substitutions are performed at various restriction sites to produce a recombinant adenovirus (claim 23). The specification does not disclose the relative location of restriction sites in other serotypes. Alternatively, the specification does not teach the relatedness of the adenoviral restriction maps such that one of skill in the art would be able to identify with precision the location of the correlative sites in the genus of recited adenovirus. By modifications at specific restriction sites in which the sites are assigned according to Ad5, the relationship between structure and function is unclear. Neither applicant nor the prior art provide a correlation between the structure of the recited restriction sites and their ability to tolerate modifications. Therefore, it must be considered that any composition comprising the recited nucleic acids must be empirically determined. In an unpredictable art, the disclosure of one example would represent to the skilled artisan that applicants were not in possession of claimed genus.

The claims furthermore, recite that the cell binding ligand can be a fragment of a monoclonal antibody or a T cell receptor. The specification only discloses use of a cloned T-cell receptor (scTCR) but do not disclose fragments of TcR that would function as cell binding ligands. Furthermore, the specification discloses use of a single chain fragment of G250 as well as monoclonal G250 (see e.g. page 6, line 15-31) and hinge regions of mouse immunoglobulin and IgG3 (see e.g. page 12, line 16-24) thus only single chain fragments and hinge regions have been disclosed. Furthermore, applicants have not described in detail the structural requirements nor described the genus of fragments of T-cell receptors and of monoclonal antibodies such that one

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of skill in the art would be able to identify with precision the fragments that would be able to function as cell binding ligands. Given the large size of fragments of T-cell receptors and of monoclonal antibodies and the diverse nature of these fragments and the lack of guidance as to the structural requirements of these fragments to provide cell-binding function, it is concluded that the invention must be empirically determined. Therefore, it must be considered that any composition comprising the recited nucleic acids must be empirically determined. In an unpredictable art, the disclosure of two examples would represent to the skilled artisan that applicants were not in possession of claimed genus.

Furthermore, the claims recite inclusion of a sequence that increases the survival of the fiber in the cytosol of infected cells, thereby enhancing the transportation into the nucleus and virus assembly. Furthermore, the claims recite that the sequences are present in the wild-type knob. Aside from the recitation that the sequence can be SEQ ID NO: 10-12, applicants do not describe the sequences that would function to enhance adenovirus survival nor describe in detail the structural requirements such that one of skill in the art would be able to identify survival sequences. Given the lack of guidance as to the structural requirements of sequences that provide survival for the adenovirus and the vague and diverse nature of the functional requirements, it is concluded that the invention must be empirically determined. Therefore, it must be considered that any composition comprising the recited nucleic acids must be empirically determined. In an unpredictable art, the disclosure of no examples would represent to the skilled artisan that applicants were not in possession of claimed genus.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for structural modification performed by DNA technology, does not reasonably provide enablement for chemical or immunological means at the virus level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The invention is directed to methods treating disease of human disease with the adenovirus of the instant invention *in vivo*. The invention utilizes disciplines of molecular biology, cell biology and clinical technology.

2) Scope of the invention. The scope of the invention is broad in that the methods recite treatment of any human disease. Furthermore, the instant invention recites that the structural modifications are preformed by chemical and immunological modifications at the virus level. However, the instant claims state that the native knob has been removed. It is not clear how modification by chemical or immunological means can replace the native knob domain. The broad scope of the claims and lack of guidance exacerbates an unpredictable method.

3) Number of working examples and guidance. The specification is directed toward a method of producing an adenoviral vector by substitution of the fiber coding functions. Specifically, the trimerization and cell binding functions are replaced by heterologous sequences. Applicants do not disclose any methods for treatment of disease. Furthermore, applicants do not identify disease targets.

Furthermore, applicants provide no examples of modification of the adenovirus fiber by chemical or immunological means. It is not clear what is exactly encompassed by the use of chemical and immunological means to modify the fiber by replacing the known trimerization and cell-binding domain with a heterologous trimerization domain and cell-binding ligand.

4) State of Art. The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? Administration of nucleic acids utilizes the art of gene therapy,

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which is a highly unpredictable art. Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Deiry, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma and Somia (1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". Approaches to prolong transgene expression have proven futile in the face of the host immune response to the recombinant adenovirus (see e.g. Kmiec, page 243).

No modes of gene administration were proposed in the specification including means and routes of administration except to generally refer to gene expression vectors and retrovirus. To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and use the claimed invention for the recited treatments.

Miller and Vile teach that (FASEB, J. page 195) virions chemically modified were covalently linked to an asialoglycoprotein polylysine conjugate. It is not clear how this modification would result in a deletion of the native knob and trimerization domain. Therefore, it is highly unpredictable that chemical or immunological means of generating chimeric fibers would function to meet the limitations of the instantly recited claims.

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5) **Unpredictability of the art.** The unpredictable nature of methods treating disease of human disease with the adenovirus of the instant invention *in vivo* is exacerbated due to the lack of recited methods. Many parameters must be addressed for *in vivo* gene or protein delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. However, applicants do not propose any methods or target disease.

6) **Summary.** The invention recites a methods treating disease of human disease with the adenovirus of the instant invention *in vivo*. The unpredictability of using the claimed invention in therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbates a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-9, 11-15 and 19 are rejected under 35 U.S.C. 102(e) and 102(a) as being anticipated by Wickham et al (5,770,442; see entire document).

Wickham teach the generation of a chimeric fiber protein in which the trimerization domain and the cell-binding domain of Ad5 is replaced with that of a variety of adenoviral serotype fiber protein coding sequences such as Ad2 or Ad7. The fiber sequences of Ad2 are inserted into the N-terminus of the shaft of Ad5 but mostly downstream of the fiber shaft repeats (see e.g. figure 8). Furthermore, the fiber can comprise insertion of nonnative sequences into the native fiber sequence (see e.g. col 5, line 15-37). These include sequences that enable trimerization (line 24-30) as well as protein specific amino acid sequence that bind to target receptors such as antibodies (see e.g. col 6, line 8-25). For example chimeric fibers comprising the trimerization domain from heat shock factor protein of *K. lactis* fused with a glycine linker and RGD peptide specific for integrin (see e.g. col 14, example 5). In the case of the ad7/ad5 chimera a linker was inserted on either end of the inserted DNA (see e.g. col 15, line 4-12). Applicants have recited that the fiber includes a sequence, which increases the survival of the fiber in the cytosol. Applicants have not defined this sequence. However, there are a variety of sequences that could be envisioned to provide this function for the adenovirus such as the nuclear localization sequence (nls) that is resident at the N-terminus of the fiber and belongs to the native ad5 fiber. As well, the Ad5:HSF:RGD recombinant protein has RGD sequences that can be said to lead to survival of the virus for the same reason.

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Claims 1-4, 9, 11, 12, 15, 16, 19 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel and Krasnykh (US 6,21,946 B1; see entire document).

Curiel and Krasnykh teach the generation of modified adenovirus containing fiber replacement proteins to alter the tropism of the virus (see e.g. abstract). Ligands are incorporated into the fiber protein, which comprises the N-terminus of the adenovirus fiber gene and the C-terminus of the T4 bacteriophage fibritin gene, or another other coiled coil structure from structural, viral or transcription factor trimeric proteins (see e.g. col 3, line 42-63). As well, the fiber comprises a ligand that is selected from the group of ligands and anti-receptor antibodies (see e.g. col 4, line 4-10). A knobless Fiber-fibritin protein was generated in which the first two shafts of the fiber protein were retained and a linker connecting a 6X His ligand (see e.g. col 9, line 41 through col 10, line 35). Applicants have recited that the fiber includes a sequence, which increases the survival of the fiber in the cytosol. Applicants have not defined this sequence. However, there are a variety of sequences that could be envisioned to provide this function for the adenovirus such as the nls that is resident at the N-terminus of the fiber and belongs to the native ad5 fiber.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al (5,770,442; see entire document) or Curiel and Krasnykh (US 6,21,946 B1; see entire document) in view of Goldenberg et al (US 2003.0099629; see entire document).

Applicants recite a recombinant adenovirus comprising a replacement in the fiber protein such that an external trimerization motif and a new cell ligand-binding domain are inserted in place of the native components. Additionally, the claims recite use of an amino acid linker derived from Staphylococcus protein A.

The teachings of Wickham et al and Curiel and Krasnykh are as above except:

Wickham et al and Curiel and Krasnykh do not teach use of an amino acid linker derived from Staphylococcus protein A.

Goldenberg et al teach construction of construct with linkers such as the 13 amino acid sequence from Staphylococcal protein A to allow for flexible linkage between two sequences (see e.g. page 6, paragraph 0071).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include in the vector taught by Wickham et al and Curiel and Krasnykh the linker taught by Goldenberg because Wickham et al and Curiel and Krasnykh teach that it is within the ordinary skill of the art to generate recombinant adenovirus with fusion proteins encoded in the fiber protein and because Goldenberg et al teach that it is within the ordinary skill of the art to insert a linker between two sequences of a fusion. One would have been motivated to do so in order to receive the expected benefit of flexible linkage between the two coding sequences to allow for improved functionality of each domain. Based upon the teachings of the cited

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references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al (5,770,442; see entire document) or Curiel and Krasnykh (US 6,21,946 B1; see entire document) in view of Tattanahalli and Sahat (US 2002/0155095; see entire document).

Applicants recite a recombinant adenovirus comprising a replacement in the fiber protein such that an external trimerization motif and a new cell ligand-binding domain are inserted in place of the native components. Additionally, an external nuclear localization sequence is inserted into the adenovirus fiber.

The teachings of Wickham et al and Curiel and Krasnykh are as above except:

Wickham et al and Curiel and Krasnykh do not teach addition of a nuclear localization signal.

Tattanahalli and Saha teach the construction of composition for the delivery of interferon polypeptides. The vector can be adenoviral fiber sequences that have been altered to comprise a nuclear localization signal form SV40 (see e.g. page 7, paragraph 0064).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include in the vector taught by Wickham et al and Curiel and Krasnykh the SV40 nuclear localization taught by Tattanahalli and Sahat because Wickham et al and Curiel and Krasnykh teach that it is within the ordinary skill of the art to generate recombinant adenovirus that have been altered by the addition of external motifs to the fiber and because Tattanahalli and Sahat teach that it is within the ordinary skill of the art to add a nls to generate recombinant

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adenovirus. One would have been motivated to do so in order to receive the expected benefit of enhanced nuclear translocation for reduced exposure to the cytosol. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

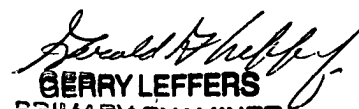
No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636


GERRY LEFFERS
PRIMARY EXAMINER

December 10, 2004